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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,029	06/09/2006	Gabriela Chiosis	MSK.P-072	1546

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,029	CHIOSIS ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *18-31,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-17 and 32-36, in the reply filed on August 20, 2007 is acknowledged. Applicants' elections of the species of breast cancer cells (claim 5) and SKBr3 cells and MCF7 cells (claim 8) are also acknowledged. Claims 18-31, 39 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claim 8 has been amended. No claims have been canceled. Claims 37-40 have been added. Accordingly, claims 1-17 and 32-38 are examined on the merits herewith.

In their traversal, Applicants state that they disagree that the claims lack a common technical feature and that all of their inventions should be examined under PCT practice. Applicants discuss the features that are common to pairs of inventions listed in the restriction requirement Office action and assert that no double patenting rejection would be allowable between Groups I and II. Applicants assert that Examiner did not explain how the Hsp90 inhibitor geldanamycin renders the method inventions obvious and that, with respect to Group III, the cited art does not disclose fluorescently labeled geldanamycin.

In reply, it was explained clearly in the previous Office action that, for unity of invention to be present, a common special technical feature must be present in each invention listed. The technical feature that links the different inventions is an Hsp90 inhibitor, and this technical feature is not special, because Hsp90 inhibitors such as geldanamycin are known. It was also explained that, in a case where a special technical feature is present, the combination of inventions that will be examined together if Group I is a method of using a composition is Group I plus the composition, plus a method of making that composition if such method claims are

present. Double patenting and whether or not one invention renders another obvious are not criteria under unity of invention practice.

In view of the foregoing, the restriction is deemed proper and is made final.

Claim Objections

Claim 7 is objected to because of the following informality- it contains a grammatical error. The claim recites that the different cell types includes cells selected from a particular group. The claim has a plural subject and a singular verb (the different cell types include cells from ... group). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites that the different cell types have at least partially different Hsp90-dependent activity, which renders the meaning of the claim unclear. The Hsp90-dependent activity of two types of cells is either the same or different. It cannot be partially different or at least partially different. Moreover, the activities of the two cell types must be different for the assay to work and distinguish between the two (otherwise it is of no use to use more than one cell type). Appropriate correction is required. The words "at least partially" may be deleted.

Claim 32 recites "... wherein the molecule via the binding moiety to Hsp90, and the fluorescent moiety has polarized fluorescence when the compound is bound to Hsp90, and

fluorescence with a lesser degree of polarization when the compound is not bound to Hsp90." This clause is confusing, rendering the claim unclear. Applicants may mean "... wherein the binding moiety binds to Hsp90, the fluorescent moiety has polarized fluorescence when the compound is bound to Hsp90, and the fluorescent moiety has a lesser degree of polarization when the compound is not bound to Hsp90." Applicants' exact meaning cannot be determined. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 and 32-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gewirth et al. (US 2002/0160496 A1) in view of Rosen et al. (WO 02/094196 A2); Chiosis et al. ("A small molecule designed to bind to the adenine nucleotide pocket of Hsp90 causes Her2 degradation and the growth arrest and differentiation of breast cancer cells," Chem & Biol 8:289-299, 2001; Devlin et al. (US 6,060,598); Bennett et al. (US 4,902,630) and Pagé et al.

(US 5,981,564).

The claimed method is a two-part method for screening candidate molecules for Hsp90 inhibitor activity. The first part, claim 1, recites a competitive ligand binding assay, in which a potential ligand competes with a known, labeled ligand for binding to Hsp90, and binding is determined by measuring a reduction in fluorescence relative to a negative control (no candidate molecule present). The second part, claim 3, recites an assay to test the biological activity of Hsp90 ligands. A candidate molecule that is an Hsp90 ligand is incubated with cells that have an Hsp90-dependent activity (the specification makes it clear that this activity is Her2 expression), and an inhibition of this activity is measured relative to a negative control (cells that are not contacted with the Hsp90 ligand).

Regarding claims 1-4 and 12, Gewirth et al. disclose a screening method for identifying candidate molecules that are inhibitors of Hsp90 activity. In this method, a sample comprising Hsp90 is combined with a candidate substance. A fluorescently labeled compound that is a ligand for Hsp90 (8-ANS, 1,8-anilinonapthalene sulfonate, an ansamycin) is added to the mixture. The fluorescence signal produced by the ligand in the sample and candidate-containing mixture is then detected and compared to that of a control mixture containing no candidate (see paragraphs 283-289). Binding of the inhibitor reduces the signal produced by bound labeled ligand. This difference in signals allows for detection of inhibitor binding. This assay may also be a cell-based screening assay, as the samples may comprise cells, including human cells, that express Hsp90. Various cell types may be used in the assay, such as cells that express Hsp90 recombinantly, mammalian cells and yeast cells (see paragraphs 292 and 295). These cells may be tumor cells. Anti-tumor agents whose Hsp90 binding activity may be tested are also disclosed. These agents inhibit the proliferation of tumor cells (see paragraph 301). Thus, this assay may be used to screen for anti-tumor activity.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to perform the two assay types of Gewirth et al., the ligand binding assay and the biological activity assay, in sequential order, because both types of assays were conventional in the art at the time of the invention. One of ordinary skill in the art would have known that assays involving test compounds (candidate molecules) and proteins only, with no live cells present, would have been quicker, easier and simpler to perform than assays involving cells. One of ordinary skill in the art would have expected that, in performing the first assay on a large group of test compounds/molecules, he would have identified two sets of compounds/molecules, those that bound to Hsp90 and those that did not, and he would have known that only the compounds/molecules that bound to Hsp90 would have been worth testing for their biological activity.

Gewirth et al. do not disclose that the detectable fluorescence of bound and unbound label may be measured as the degree of polarized fluorescence. Gewirth et al. also do not disclose that the cells in their assay for biological activity are two different types of breast cancer cells. Gewirth et al. do not disclose that their labeled ligand is FITC- or BODIPY-labeled geldanamycin.

Regarding claims 5-7 and 9, Rosen et al. disclose that overexpression of Her2 is related to hyperproliferative disorders, especially breast cancer. In breast cancer patients that overexpress Her2, administration of a therapeutic amount of an Hsp90 inhibitor is desirable to treat the disease (see paragraph bridging pp. 3 and 4). Thus, as these cells respond to Hsp90 inhibitors, they also express Hsp90. The sensitivity of the cancer cells to an ansamycin that is a type of geldanamycin (CNF-101 or 17-AAG) is proportional to Her2 level in those cells (see p. 3, third full paragraph). Administration of an Hsp90 inhibitor may be in vivo or ex vivo. Testing of patient samples may also be performed to measure the sensitivity of the patient's

cells to one or more Hsp90 inhibitors prior to administration of an Hsp90 inhibitor as a therapeutic. With respect to testing different cell types, such as different types of breast cancer cells that express Hsp90 protein, or normal and abnormal cells, this testing may be done on abnormal and normal cells and with positive and negative controls (see p. 4 and p. 7, last paragraph). Thus, multiple Hsp90 inhibitors may be tested with a patient's breast cancer cells and non-cancerous cells to determine which one would be the most potent inhibitor, while also providing an indication of toxicity to normal cells. One of ordinary skill in the art at the time that the invention was made would have been motivated to use breast cancer cells with an elevated expression level of Her2 in the screening assay of Gewirth et al., because Rosen et al. teach that when an Hsp90 inhibitor is administered to Her2-expressing cells, which also express Hsp90, the inhibitor binds and inhibits the activity of Hsp90. One of ordinary skill in the art would have known that the cells of Rosen et al. would have worked in the assay of Gewirth et al. Also, one of ordinary skill in the art would have been motivated to use Her2-expressing breast cancer cells in the assay of Gewirth et al. as a method of identifying new Hsp90 inhibitors that would be new breast cancer drugs, a type of drug for which there is strong need.

Regarding claim 8, Rosen et al. disclose that SKBR-3 cells are a breast cancer cell line that expresses a high level of Her2 and that is sensitive to geldanamycin (17-AAG). MCF-7 cells are a breast cancer cell line that expresses a low level of Her2 and that is resistant to geldanamycin ((17-AAG) (see p. 10, Example 1; p. 13, third full paragraph and Fig. 1). It would have been obvious to one of ordinary skill in the art to use these cell lines in the biological activity assay of Gewirth et al., because Rosen et al. disclose that these cells lines are commercially available and may be used to test the activity of anti-cancer drugs. Thus, one of ordinary skill in the art would have had a strong expectation of success in using these cell lines in a biological activity assay to identify anti-cancer compounds or molecules that inhibit the

growth of these two cell types. One of ordinary skill in the art would also have recognized the value of screening for drugs that inhibit the growth of breast cancer cells that do not respond to known drugs, such as geldanamycin.

Regarding claims 10-13, Chiosis et al. disclose that Hsp90 is a family of chaperone proteins having four members, Hsp90 alpha, Hsp90 beta, Grp94 and Trap-1. These proteins are overexpressed in tumors and possess a unique pocket at the N-terminus that is specific and conserved among the family members but not found in other chaperone proteins (see p. 289 and p. 293, first full paragraph). Thus, one of ordinary skill in the art at the time that the invention was made would have expected to have been able to use any one of the Hsp90 protein family members in the assays of Gewirth et al.

Regarding claim 17, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to use a saturating amount of the known, labeled ligand in the competitive ligand binding assay, because one of ordinary skill in the art would have known that this was a necessary experimental parameter. He would have known that if this amount were not saturating, it would not have been possible to distinguish between an amount of bound fluorescence (or polarized fluorescence) that is lower because the test compound also bound and an amount that was lower because some of the Hsp90 ligand binding sites were empty (i.e., too little labeled ligand present).

Regarding claims 14-16 and 32-38, as noted above, Gewirth et al., Rosen et al. and Chiosis et al. disclose that the geldanamycin 17-AAG is a ligand for Hsp90 and the Hsp90 family (see Chiosis et al., p. 290).

Devlin et al. disclose that assays with a fluorescent label that are homogeneous (bound label need not be separated from free label before measurement because the signals of the bound label and free label are different) suffer from the disadvantages that they are not

sensitive and have a high background (see col. 3, lines 49-56, and col. 4, lines 53-67). Labels like fluorescein, however, can emit polarized light, and the dependency of polarization on molecular size can be exploited in assays with a fluorescein labeled compound, such as a drug, to determine the presence or amount of the drug (see col. 5, line 29, to col. 6, line 14). Fluorescein labels may be used in fluorescence polarization assays. Fluorescence polarization assays have the advantages of homogeneous assays (simpler, fewer steps, no need to separate unbound label) and the advantage that they are not dependent on light intensity, fluctuations in which typically cause assay variability (see col. 6, lines 39-54). Also, the degree of polarization of the labeled compound is proportional to the sensitivity of the assay (see col. 17, lines 28-31). As a result, selection of a highly polarizing label yields an assay with improved sensitivity compared to other fluorescence assays. Bennett et al. disclose that fluorescence polarization assays may also be performed in which the polarizing fluorescent label is bound to a relatively large molecule such as protein (see col. 3, lines 41-49; col. 4, lines 22-36; and col. 7, lines 16-34). Prior to Bennett et al., it had been thought that such assays would work only when the label was bound to a relatively small molecule (see col. 2, lines 49-63). Bennett et al. disclose several examples of fluorescent labels that emit polarized light when bound, e.g., FITC (fluorescein isothiocyanate) (see col. 1, line 50, to col. 2, line 2). Pagé et al. disclose that FITC and BODIPY are functional equivalents in that both are fluorescent labels that may be used in fluorescence polarization assays (see col. 20, lines 20-34).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use a fluorescence polarization technique, as disclosed by Devlin et al. and Bennett et al., for determining the amount of inhibitor binding to Hsp90 in the assays of Gewirth et al., rather than other types of fluorescence measurements, because Bennett et al. teach that polarizing fluorescent labels may be used with relatively large molecules, such as proteins. It

would have been obvious to use FITC or BODIPY as the fluorescent label, because Bennett et al. teach the FITC label, while Pagé et al. teach both labels. Devlin et al. teach that fluorescence polarization assays have the advantages of sensitivity and reproducibility, without the need to separate free from bound label (i.e., a homogeneous assay may be performed).

In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2007-08-28

Rosanne Kosson

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PRIMARY EXAMINER
GROUP 1600